REMARKS

Claims 23 and 28 were canceled. Therefore, claims 19-21, 24-27, and 29 are pending.

In response to the Examiner's comments, claim 19 was amended to include the limitation of cancelled claim 23, and claims 24-25 and 29 were amended to correct dependency. No new matter is added by the above amendments.

I. Formal Matters and Objections

A. The Draftsperson objected to the drawings, as noted on the Drawing Review. Applicants assure the Examiner that corrected drawings will be submitted by the Applicant as soon as they are received by the undersigned.

B. Regarding the IDS, two references listed were not considered because the IDS did not contain copies of those references (AK: Brixey et al. (1993) J. Clin. Psychol. 49:447-56 and BF: Grice (1996) Am. J. Hum. Genet. 59:644-52). Applicants apologize for the error. Enclosed are copies of the missing references.

C. The Examiner objected to the specification on the basis that it contained an inbedded hyperlink at page 34. Accordingly, the specification is amended above to delete the hyperlink.

II. Rejections Under 35 USC § 112, first paragraph.

Claims 22-29 were rejected for lack of written description on the basis that claim 22 limits a binary linear regression to be performed by an "SAS system" which is not described in the specification, nor is "SAS" defined.

Applicants respectfully traverse this rejection on the grounds that the term "SAS system" is well understood by one of skill in the art, and the applicants are not required to describe in the specification was is already publicly known and available in the art. A method of performing a binary regression with a SAS system was publicly available prior to the effective filing date of this application, as evidenced by the Proprietary Software Release program 6.12 TS060, by SAS Institute, Inc., Cary, NC, copyrights 1989-1996. Accordingly, in light of these remarks, it is believed that this rejection may now be withdrawn.

III. Rejections Under 35 USC § 112, second paragraph.

Claims 22-29 were rejected as indefinite for reciting the phrase "SAS system." Applicants respectfully traverse this rejection. The above remarks addressing the rejection of claim 22 under the first paragraph of §112 is fully relevant to this rejection, and is herein specifically incorporated by reference. Accordingly, it is believed that this rejection should be withdrawn.

IV. Rejections Under 35 USC § 103(a)

Claims 19-21 were rejected as obvious over Whitehead (QJM (1995) 88:763-766) in view of Weinberg et al. (1988) Am. J. Hum. Genet. 62:969-978, and Chatkupt et al. (1992) Am. J. Med. Genet. This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

The invention as claimed. Claim 19 was amended to incorporate the limitation of cancelled claim 23. Thus amended claim 19 is drawn to a method of estimating the susceptibility of an individual to have offspring that develop a developmental disorder comprising: (a) collecting a biological sample from one or more participants; wherein a participant is either the individual or a blood relative of the individual; and wherein the biological sample contains nucleic acids and/or proteins of the participant; (b) analyzing the nucleic acids and/or proteins from the biological sample; wherein said analyzing results in a partial or full genotype for the alleles of the genes involved in folate, pyridoxine, and/or cobalamin metabolism; and wherein said partial or full genotype forms a dataset of genetic explanatory variables for the participants; (c) adding the datasets of genetic explanatory variables obtained from steps (a) and (b) to a genetic reference dataset therein forming a combined genetic dataset; (d) formulating a model comprising the genetic explanatory variables obtained from the

participants; and (e) analyzing the combined genetic dataset by binary logistic regression; wherein a predicted probability for the individual to have offspring that develop a developmental disorder is determined, wherein the genetic and environmental susceptibility of an individual to have offspring that develop a developmental disorder is estimated, and wherein the individual is a pregnant woman.

Claim 20 adds the further step of: (f) modifying the model by adding or subtracting a genetic explanatory variable; and re-analyzing the combined genetic dataset by binary logistic regression; wherein a model is chosen that best fits the data.

Claim 21 adds the further step of: (g) testing the model for goodness of fit.

The Whitehead et al. reference. Whitehead et al. studied the relationship of the gene for 5, 10 methylene tetrahydrofolate reductase in relation to the occurrence of neural tube defects (NTD), and found a high incidence for the thermolabile allele with NTD when analyzed by logistic regression analysis.

The Weinberg et al. reference. Weinberg et al. describe a log-linear method for analyzing disease genes to fetal and parental characteristics.

The Chatkupt et al. reference. Chatkupt et al. discuss the role of genomic imprinting, the expression of a gene depending on whether it is transmitted through the male or female parent, on spina bifida.

The analysis required under § 103(a). The rejection is respectfully traversed on the grounds that the combined references do not render the instant invention obvious and that the Examiner has failed to establish a *prima facie* case of obviousness. The Whitehead et al. reference does not render the instant invention obvious because Whitehead et al. do not distinguish between mother and father, and thus are not able to estimate the susceptibility of a pregnant woman to have an offspring with a developmental disorder, or to provide a method for doing so. Applicants submit that speculation that "genetic screening could identify women who will require folic acid supplements to reduce their risk of having a child" with neural tube defects (abstract) do not provide a method as claimed by the instant invention.

The defects of the Whitehead et al. reference are not cured by the combination with Weinberg et al. While Weinberg et al. do look at the maternal effect, they do not review a single disorder, e.g., such as folate, and do not identify a gene-teratogen model, as provided by the instant invention.

The Chatkupt et al. reference relates to the concept of genetic imprinting, a concept which is not at all related to the instant invention. Accordingly, it is not believed that Chatkupt et al. is either relevant to the instant invention or combinable with Whitehead et al. and Weinberg et al.

The Examiner's rejection appears to be based on use of the instant specification as a guide to selecting elements out of the cited references without any suggestion or instructions in the cited references for selecting and combining elements. It is recognized that selecting elements out of prior art references in the absence of a specific teaching or suggestion within the references to do so cannot form the basis of a rejection under § 103(a). In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987). Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, and in light of the above amendments and remarks, this rejection should be withdrawn.

Conclusion

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

In the event that there are any questions concerning this Amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,
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Date: 5 August 2002

Marked up Version showing changes made

In the specification:

The paragraph at page 34, line 18 to page 35, line 3:
There are many methods currently known in the art to identify variant/mutant DNA, all of which may be used in the present invention [(*see e.g.*, internet address http://www.ich.bpmf.ac.uk/cmgs/mutdet.htm)]. Such methods include but in no way are limited to direct sequencing, array sequencing, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Malditof) [Fitzgerald *et al.*, *Ann. Rev. Biophy. Biomol. Struct.* 24:117-140 (1995)], Polymerase Chain Reaction "PCR", reverse-transcriptase Polymerase Chain Reaction "RT-PCR", RNAase protection assays, Array quantitation *e.g.*, as commercially provided by Affymetrix, Ligase Chain Reaction or Ligase Amplification Reaction (LCR or LAR), Self-Sustained Synthetic Reaction (3SR/NASBA), Restriction Fragment Length Polymorphism (RFLP),Cycling Probe Reaction (CPR), Single-Strand Conformation Polymorphism (SSCP), heteroduplex analysis, hybridization mismatch using nucleases (*e.g.*, cleavase), Southern, Northerns, Westerns, South Westerns, ASOs, Molecular beacons, footprinting, and Fluorescent *In Situ* Hybridization (FISH). Some of these methods are briefly described below.

In the claims:

19. (Amended Once) A method of estimating the susceptibility of an individual to have offspring that develop a developmental disorder comprising:

(a) collecting a biological sample from one or more participants; wherein a participant is either the individual or a blood relative of the individual; and wherein the biological sample contains nucleic acids and/or proteins of the participant;

(b) analyzing the nucleic acids and/or proteins from the biological sample; wherein said analyzing results in a partial or full genotype for the alleles of the genes involved in folate, pyridoxine, and/or cobalamin metabolism; and wherein said partial or full genotype forms a dataset of genetic explanatory variables for the participants;

(c) adding the datasets of genetic explanatory variables obtained from steps (a) and (b) to a genetic reference dataset therein forming a combined genetic dataset;

(d) formulating a model comprising the genetic explanatory variables obtained from the participants; and

e) analyzing the combined genetic dataset by binary logistic regression;

wherein a predicted probability for the individual to have offspring that develop a developmental disorder is determined; [and] wherein the genetic and environmental susceptibility of an individual to have offspring that develop a developmental disorder is estimated, and wherein the individual is a pregnant woman.

24. (Amended Once) A method of lowering the risk of a pregnant woman who has been determined by the method of Claim [23] 21 to be susceptible to have offspring that develop a developmental disorder comprising administering methylfolate, cobalamin or pyridoxine to the pregnant woman, wherein said administering lowers the risk of the pregnant woman of giving birth to offspring with a developmental disorder.

25. (Amended Once) A method of determining if any treatment is advisable for a pregnant woman who has been determined by the method of Claim [23] 21 to be susceptible to having offspring that develop a developmental disorder comprising determining the concentration of a risk factor from a tissue sample or body fluid from the pregnant woman; wherein when the concentration of the risk factor is statistically above or below an accepted normal range, treatment is advisable.

29. (Amended Once) A method of treating an asymptomatic individual determined by the method of Claim [23] 21 to be susceptible for developing a developmental disorder comprising administering methylfolate, cobalamin or pyridoxine.